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PHILIP S. JOHNSON
JOHNSON & JOHNSON
ONE JOHNSON & JOHNSON PLAZA
NEW BRUNSWICK, NJ 08933-7003

EXAMINER	
SINGH, SATYENDRA K	
ART UNIT	**PAPER NUMBER**
1651	

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Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	10/518,987	SIX ET AL.	
	Examiner	Art Unit	
	Satyendra K. Singh	1651	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *23 May 2006*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-15* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-15* is/are rejected.

7)☒ Claim(s) *2-15* is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☒ The drawing(s) filed on *21 December 2004* is/are: a)☒ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☒ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☒ All b)☐ Some * c)☐ None of:

1.☒ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date *6/28/06*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

Applicant's response filed with the office on May 23, 2006 is duly acknowledged.

Claims 1-15 are pending in the application, and are examined on their merits in this office action.

Election/Restrictions

Applicant's election with traverse of "Eudragit E100" as an elected species (readable on claims 4, 6, and 7) in the reply filed on May 23rd 2006 is acknowledged. The traversal is on the ground(s) that the species claimed are "art recognized equivalents" used for enhancing dissolution (i.e. the technical feature) of poorly soluble drugs, and therefore the invention as claimed does not lack unity when considered as a whole (see applicant's remarks, page 2, in particular). Applicant's arguments have been found to be persuasive, and therefore, the requirement for the **election of species** (as previously set forth by the examiner) has been **withdrawn**.

Claims 1-15 have been examined as presented by applicants, hereafter.

Claim Suggestions

Claims 1 and 9 have minor typographical mistakes in the body of the claims. Claim 1 recites the limitation "**pooly**" which should be corrected to recite "poorly". Claim 9 recites the limitation "bioavailability **o** an orally administered bioactive compound" which should be corrected to "bioavailability of an orally administered bioactive compound". Appropriate correction is requested.

Claim Objections

Claims 2-15 are objected to under 37 CFR 1.75(c), as being of improper dependent form for failing to further limit the subject matter of a previous claim. Applicant is required to cancel the claim(s), or amend the claim(s) to place the claim(s) in proper dependent form, or rewrite the claim(s) in independent form. Claims 2-15 each recite "**solid dispersions**" according to the respective broader claim(s) 1, 6, or 12, which is improper and fails to further limit the subject matter of the previous claim(s). Applicant is advised to submit amended claims (for example claims reciting "**The** solid dispersions according to claim...") that properly limit the scope of the subject matter being claimed in the instant invention. Appropriate correction is required.

Claim Rejections - 35 USC § 112

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claims 3, 4, 6, 7, and 8 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claims 3, 4, 6, 7, and 8 contain one or more of the trademark/trade names viz: **Eudragit E100 and PVPVA64.** Where a trademark or trade name is used in a claim as a limitation to identify or describe a particular material or product, the claim does not comply with the requirements of 35 U.S.C. 112, second paragraph. See *Ex parte Simpson*, 218 USPQ 1020 (Bd. App. 1982). The claim scope is uncertain since the trademark or trade name cannot be used properly to identify any particular material or

product. A trademark or trade name is used to identify a source of goods, and not the goods themselves. Thus, a trademark or trade name does not identify or describe the goods associated with the trademark or trade name. In the present case, the trademark/trade name is used to identify/describe " polymers that allows enhanced dissolution" and "polymers that allow a homogeneous or molecular dispersion", respectively and, accordingly, the identification/description is indefinite. Appropriate clarification is required.

For examination purposes, claims reciting trademark/trade names (as discussed supra) have been examined as encompassing the generic chemical compounds (as well as derivatives thereof) known in the art (see prior art, Jung et al, WO 99/33467, IDS, page 7, last paragraph; Rosenberg et al, WO 02/11694 A2, IDS, page 3; and Baert et al, WO 97/44014, IDS, page 7 and claim 6, in particular).

Claim Rejections - 35 USC § 102

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

Claims 1-3, 5, 8-10, 12-15 are rejected under 35 U.S.C. 102(b) as being anticipated by Baert et al (WO 97/44014; IDS).

Claims are generally drawn to solid dispersions (i.e. a composition) comprising a poorly soluble bioactive compound dispersed in a polymeric matrix, comprising more than one polymer, characterized in that a first polymer allows a homogeneous or molecular dispersion of the bioactive compound in the polymer matrix, while a second polymer has a dissolution profile associated with the creation of a micro-environment

enhancing the dissolution of the bioactive compound in an aqueous environment (see specific recitations of instant claims 1-3, 5, 8-10, 12-15).

Baert et al (IDS) teach antifungal compositions in the form of solid dispersions having improved bioavailability in an aqueous environment such as gastric fluid (see Baert et al, abstract, page 12-13, examples 1-5, and claims, in particular), wherein the polymer matrix comprises a polymer having a stabilizing effect on the bioactive compound (such as antifungal drug, itraconazole) in solution (see page 4, 2nd paragraph, in particular), wherein the polymer allowing enhanced dissolution of the bioactive compound in an aqueous environment is hydroxypropyl methylcellulose (HPMC; see Baert et al, page 12, in particular), wherein the polymer allowing a homogeneous dispersion is crospovidone (a crosslinked polyvinylpyrrolidone, PVP, i.e. a derivative of PVP akin to PVPVA64 claimed in the instant invention; see Baert et al, page 10, 3rd and last paragraph, in particular), wherein one or more polymer matrices comprise HPMC and crospovidone. The limitations of claims 9 and 10 are explicitly taught by the referenced invention as Baert et al teach solid dispersions comprising polymer matrix that enhance bioavailability of an orally administered bioactive compound, such as a class II drug (see the disclosure provided by the applicants, page 3, lines 16-18 of the instant specification), itraconazole/saperconazole (see Baert et al, page 10, in particular).

The limitations of instant claims 14 and 15 (wherein the solid dispersions according to claim 1 are prepared by extrusion or spray drying processes; product by process claims) are met by the solid dispersions comprising itraconazole and polymer

matrices such as HPMC and crospovidone (see Baert, discussion supra) that provide enhanced bioavailability to the antifungal drug when ingested orally.

> "[E]ven though product-by-process claims are limited by and defined by the process, determination of patentability is based on the product itself. The patentability of a product does not depend on its method of production. If the product in the product-by-process claim is the same as or obvious from a product of the prior art, the claim is unpatentable even though the prior product was made by a different process." In re Thorpe, 777 F.2d 695, 698, 227 USPQ 964, 966 (Fed. Cir. 1985)

As per MPEP 2111.01, *during examination, the claims must be interpreted as broadly as their terms reasonably allow. In re American Academy of Science Tech Center, F.3d, 2004 WL 1067528 (Fed. Cir. May 13, 2004)(The USPTO uses a different standard for construing claims than that used by district courts; during examination the USPTO must give claims their broadest reasonable interpretation.). This means that the words of the claim must be given their plain meaning unless applicant has provided a clear definition in the specification. In re Zletz, 893 F.2d 319, 321, 13 USPQ2d 1320, 1322 (Fed. Cir. 1989).*

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

The factual inquiries set forth in *Graham* **v.** *John Deere Co.*, 383 U.S. 1, 148 USPQ 459 (1966), that are applied for establishing a background for determining obviousness under 35 U.S.C. 103(a) are summarized as follows:

1. Determining the scope and contents of the prior art.
2. Ascertaining the differences between the prior art and the claims at issue.
3. Resolving the level of ordinary skill in the pertinent art.
4. Considering objective evidence present in the application indicating obviousness or nonobviousness.

1. Claims 1-15 are rejected under 35 U.S.C. 103(a) as being unpatentable over Rosenberg et al (WO 02/11694 A2; IDS) in view of Baert et al (WO 97/44014; IDS) or Jung et al (WO 99/33467; IDS).

Claims are generally drawn to solid dispersions (i.e. a composition) comprising a poorly soluble bioactive compound dispersed in a polymeric matrix, comprising more than one polymer, characterized in that a first polymer allows a homogeneous or molecular dispersion of the bioactive compound in the polymer matrix, while a second polymer has a dissolution profile associated with the creation of a micro-environment enhancing the dissolution of the bioactive compound in an aqueous environment.

Rosenberg et al (IDS) teach antifungal compositions and dosage forms (such as solid dispersions suitable for application in the oral cavity) comprising a poorly bioavailable pharmaceutical active ingredient (such as itraconazole; see Rosenberg et al, abstract, page 2, lines 10-43, and claims, in particular) dispersed in a pharmaceutically acceptable matrix that can comprise of polymers such as hydroxyalkyl alkylcellulose (i.e. HPMC), or Eudragit ™, or homo- and copolymers of n-vinylpyrrolidone/vinyl acetate (similar to the polymeric matrix, PVPVA64, as claimed; see Rosenberg et al, page 3, lines 6-17, in particular). Rosenberg et al teach the solid dispersions comprising a class II drug, itraconazole and a combination of polymer matrices such as n-vinylpyrrolidone/vinyl acetate copolymer and hydroxypropyl cellulose (HPC) that provide homogeneous dispersion and enhanced solubility under aqueous conditions of the oral cavity (see Rosenberg et al, page 7, examples 1-3; page 6, lines 14-24, in particular).

However, although suggested by the prior art (see Rosenberg et al, discussion supra), solid dispersions comprising a poorly soluble bioactive compound dispersed in a combination of polymer matrices as claimed in instant claims 6 (i.e. **Eudragit E100** and

PVPVA64) and claim 8 (i.e. **HPMC** and PVPA64) is not explicitly taught by the referenced invention of Rosenberg et al.

The teachings of Baert et al (IDS) have been discussed supra, and are further relied upon in the same manner. Baert et al teach solid dispersions comprising a bioactive, antifungal compound, itraconazole and HPMC (hydroxypropyl methylcellulose) in combination with crospovidone (a crosslinked polymer of polyvinylpyrrolidone; see Baert et al, claim 18, in particular) that are suitable for enteric compositions that are administered orally.

Jung et al (IDS) teach method and composition (solid dispersions) of an oral preparation of itraconazole comprising aminoalkyl methacrylate copolymer (i.e. Eudragit E; see abstract, examples 1-7, tables 3-5, and claims, in particular) that is suitable for oral ingestion and antifungal treatment. Jung et al also suggest the use of other polymer matrices in combination with Eudragit, such as crospovidone (as diluent; see Jung et al, page 8, 3rd paragraph, in particular).

It would have been obvious to a person of ordinary skill in the art at the time this invention was made to modify the composition (i.e. solid dispersions) taught by Rosenberg et al such that the solid dispersions comprise of the poorly bioactive compound in two different polymeric matrices in combination with n-vinylpyrrolidone/vinyl acetate copolymer, such as HPMC or Eudragit, as explicitly taught by the inventions of Baert et al and Jung et al.

One of ordinary skill in the art would have been motivated at the time of invention to make such substitutions in the composition or solid dispersions of Rosenberg et al

(i.e. using HPMC or Eudragit E as polymer matrices) in order to obtain resulting composition comprising a bioactive agent of class II or class IV (in combination, such as itraconazole dispersed in a polymer matrix such as a copolymer of polyvinylpyrrolidone) as suggested by the references (Baert et al, or Jung et al) with a reasonable expectation of success. The claimed subject matter fails to patentably distinguish over the state of the art as represented by the cited references. Therefore, the claims are properly rejected under 35 U.S.C. § 103.

The limitations of claim 7 (depends from claim 6, wherein a Eudragit E100/PVPVA64 ration varies between 70/30 and 80/20) would have been a matter of routine optimization to a person of ordinary skill in the art at the time this invention was made as evident by the fact that Rosenberg et al uses various percentages of the different polymer matrices to prepare the compositions comprising itraconazole (see Rosenberg et al, examples 1-3, in particular) in order to achieve better solubility and enhanced bioavailability of the antifungal drug at the desired treatment location such as oral cavity. In addition, Baert et al disclose the preparation of solid dispersion compositions (using the same procedure or processes such as extrusion, or spray drying, as claimed in the instant invention) suitable for use in gastro-intestinal fluid (such as orally administered or ingested formulations of itraconazole) using HPMC and a derivative of crosslinked polyvinylpyrrolidone (see Baert et al, claim 18, in particular) in various ratio, thus an artisan of ordinary skill would have had a reasonable expectation of success in optimizing such ratio between polymer combinations as claimed in the instant invention.

2. Claims 1-15 are rejected under 35 U.S.C. 103(a) as being unpatentable over Baert et al (WO 97/44014; IDS) in view of Matsumoto & Zografi (Pharm. Res., 1999; IDS) and Jung et al (WO 99/33467; IDS).

Claims are generally drawn to solid dispersions (i.e. a composition) comprising a poorly soluble bioactive compound dispersed in a polymeric matrix, comprising more than one polymer, characterized in that a first polymer allows a homogeneous or molecular dispersion of the bioactive compound in the polymer matrix, while a second polymer has a dissolution profile associated with the creation of a micro-environment enhancing the dissolution of the bioactive compound in an aqueous environment.

Baert et al (IDS) teach antifungal compositions in the form of solid dispersions having improved bioavailability in an aqueous environment such as gastric fluid (see Baert et al, abstract, page 12-13, examples 1-5, and claims, in particular), wherein the polymer matrix comprises a polymer having a stabilizing effect on the bioactive compound (such as antifungal drug, itraconazole) in solution (see page 4, 2nd paragraph, in particular), wherein the polymer allowing enhanced dissolution of the bioactive compound in an aqueous environment is hydroxypropyl methylcellulose (HPMC; see Baert et al, page 12, in particular), wherein the polymer allowing a homogeneous dispersion is crospovidone (a crosslinked polyvinylpyrrolidone, PVP, i.e. a derivative of PVP akin to PVPVA64 claimed in the instant invention; see Baert et al, page 10, 3rd and last paragraph, in particular), wherein one or more polymer matrices comprise HPMC and crospovidone. The limitations of claims 9 and 10 are explicitly taught by the referenced invention as Baert et al teach solid dispersions comprising polymer matrix that enhance bioavailability of an orally administered bioactive compound, such as a class II drug (see the disclosure provided by the applicants, page 3, lines 16-18 of the instant specification), itraconazole/saperconazole (see Baert et al,

page 10, in particular). The limitations of instant claims 14 and 15 (wherein the solid dispersions according to claim 1 are prepared by extrusion or spray drying processes; product by process claims) are also met by the solid dispersions comprising itraconazole and polymer matrices such as HPMC and crospovidone (see Baert, discussion supra) that provide enhanced bioavailability to the antifungal drug when ingested orally.

However, solid dispersions comprising a poorly soluble bioactive compound dispersed in two different polymer matrices such as PVPVA64 in combination with HPMC, or in combination with Eudragit E100 are not explicitly disclosed by the referenced invention of Baert et al.

Matsumato & Zografi (IDS) disclose the use of polyvinylpyrrolidone derivatives including PVP/VA64 (akin to the crosslinked polymer, crospovidone used by Baert et al) in the preparation of solid dispersions of indomethacin (a poorly soluble drug in aqueous solutions; see Matsumato & Zografi, page 1722, materials & methods, and conclusions, page 1728, in particular) in order to enhance the solubility and bioavailability of the drug.

Jung et al (IDS) teach method and composition (solid dispersions) of an oral preparation of itraconazole comprising aminoalkyl methacrylate copolymer (i.e. Eudragit E; see abstract, examples 1-7, tables 3-5, and claims, in particular) that is suitable for oral ingestion and antifungal treatment. Jung et al also suggest the use of other polymer matrices in combination with Eudragit, such as crospovidone (as diluent; see Jung et al, page 8, 3rd paragraph, in particular).

It would have been obvious to a person of ordinary skill in the art at the time this invention was made to modify the composition taught by Baert et al (i.e solid dispersions comprising itraconazole comprising two different polymer matrices such as crospovidone and HPMC) such that it comprises of a polymer such as PVPVA64 as taught by Matsumoto & Zografi, and such that it comprises of Eudragit E as explicitly taught by Jung et al for the preparation of compositions suitable for oral administration and for enhancing the bioavailability in the aqueous environment such as gastro-intestinal tract.

One of ordinary skill in the art would have been motivated at the time of invention to make this kind of modification (i.e. substitution in the polymer matrices, and combinations thereof) in order to obtain suitable solid dispersions with enhanced bioavailability in aqueous environments such as gastric juice or intestinal environment as suggested by the references with a reasonable expectation of success. Since, all the components of composition (i.e. solid dispersions made by extrusion or spray drying processes) as claimed are taught by the referenced inventions of Baert et al (in combination with the disclosures from Matsumoto & Zografi and Jung et al), the claimed subject matter fails to patentably distinguish over the state of the art as represented by the cited references. Therefore, the instant claims are properly rejected under 35 U.S.C. § 103.

The limitations of claim 7 (depends from claim 6, wherein a Eudragit E100/PVPVA64 ration varies between 70/30 and 80/20) would have been a matter of routine optimization to a person of ordinary skill in the art at the time this invention was

made as evident by the fact that Baert et al disclose the preparation of solid dispersion compositions (using the same procedure or processes such as extrusion, or spray drying, as claimed in the instant invention) suitable for use in gastro-intestinal fluid (such as orally administered or ingested formulations of itraconazole) using HPMC and a derivative of crosslinked polyvinylpyrrolidone (see Baert et al, claim 18, in particular) in various ratio, thus an artisan of ordinary skill would have had a reasonable expectation of success in optimizing such ratio between polymer combinations as claimed in the instant invention.

> "[E]ven though product-by-process claims are limited by and defined by the process, determination of patentability is based on the product itself. The patentability of a product does not depend on its method of production. If the product in the product-by-process claim is the same as or obvious from a product of the prior art, the claim is unpatentable even though the prior product was made by a different process." In re Thorpe, 777 F.2d 695, 698, 227 USPQ 964, 966 (Fed. Cir. 1985)

As per MPEP 2144.06, *In order to rely on equivalence as a rationale supporting an obviousness rejection, the equivalency must be recognized in the prior art, and cannot be based on applicant's disclosure or the mere fact that the components at issue are functional or mechanical equivalents. In re Ruff, 256 F.2d 590, 118 USPQ 340 (CCPA 1958).*

As per MPEP 2144.06, "*It is prima facie obvious to combine two compositions each of which is taught by the prior art to be useful for the same purpose, in order to form a third composition to be used for the very same purpose.... [T]he idea of combining them flows logically from their having been individually taught in the prior art." In re Kerkhoven, 626 F.2d 846, 850, 205 USPQ 1069, 1072 (CCPA 1980).*

As per MPEP 2144.05 [R3], II. OPTIMIZATION OF RANGES - A. Optimization Within Prior Art Conditions or Through Routine Experimentation: *Generally, differences in concentration or temperature will not support the patentability of subject matter encompassed by the prior art unless there is evidence indicating such concentration or temperature is critical. "[W]here the general conditions of a claim are disclosed in the prior art, it is not inventive to discover the optimum or workable ranges by routine experimentation." In re Aller, 220 F.2d 454, 456, 105 USPQ 233, 235 (CCPA 1955).*

Conclusion

NO claims are allowed.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Satyendra K. Singh whose telephone number is 571-272-8790. The examiner can normally be reached on 9-5MF (alternate Fridays OFF).

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Michael Wityshyn can be reached on 571-272-0926. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

Satyendra K. Singh
Patent Examiner
Art Unit 1651

SANDRA E. SAUCIER
PRIMARY EXAMINER